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| 10/551,649 | 09/29/2005 | Yechezkel Barenholz | BARENHOLZ9A | 5688 |

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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

| EXAMINER | |
|---|---|
| SHOMER, ISAAC | |

| ART UNIT | PAPER NUMBER |
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| 1612 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/551,649 | BARENHOLZ ET AL. | |
| | Examiner | Art Unit | |
| | ISAAC SHOMER | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8,10,11,13,14,16-20,26 and 54* is/are pending in the application.

4a) Of the above claim(s) *17-20 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10-11, 13-14, 16, and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Group IV, claim 26, is rejoined with Group I and will be substantively examined.

Applicant's election with traverse of Group I, claims 1-8, 10-11, 13-14, and 16 in the reply filed on 18 May 2009 is acknowledged. The traversal is on the ground(s) that:

1. There is no lack of unity because the claims common to both groups serve to define the same or corresponding technical feature.

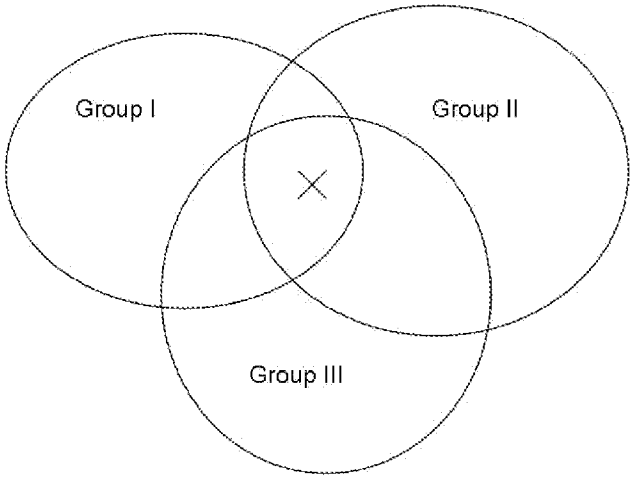
2. Requiring restriction among groups including the same claims is prohibited by a line of cases including In re Weber et al.

This is not found persuasive because for the following reasons:

1. The examiner points out that to establish lack of unity, it is necessary to show that the special technical feature shared by the groups does not make a contribution over the prior art. PCT Rule 13.2 defines "special technical features" as "those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art." The existence of a prior embodiment reading on the union of Groups I-III, as shown in the figure infra, causes groups I-III to fail to share a special technical feature.

The special technical feature of Group I is a lipid assembly. The lipid assembly of claim 1 does not present a contribution over the prior art. As disclosed in Wei et al. (US 5,677,337) teaches, on Example 7 (column 17 lines 16-20 and column 18 lines 1-10) in view of column 13 lines 41-45 and column 13 line 67-column 14 lines 1-3, as shown

infra, the lipid assembly of instant claim 1 lacks an inventive step. As such, Group I does not share a special technical feature with the instant claims of Group II-III. Therefore, the claims are not so linked within the meaning of PCT Rule 13.2 so as to form a single inventive concept, and unity between Groups I-III is broken.




2. As to In re Weber et al. (198 USPQ 328, 331 CCPA 1978), the following opinion is given:

As a general proposition, an applicant has a right to have *each* claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. Such action would not affect the right of the applicant eventually to have each of the claims examined in the form he considers to best define his invention. If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification.

According to the opinion above, the prohibited restriction requirement is one wherein the part of a single claim is examined in one group, and a different part of the same claim is examined in a different group. This was not the intent of the restriction requirement. The intent was such that the totality of claims 1-8, 10-11, and 13 would be substantively examined whether Groups I, II, or III were elected. Furthermore, the examiner points out that the instant case is restricted under the lack of unity principle used for applications filed under 35 U.S.C. 371, whereas In re Weber et al. was in regard to a case restricted under 25 U.S.C. 121.

The requirement is still deemed proper and is therefore made FINAL.

Claims 17-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 18 May 2009.

Applicant's election with traverse of ceramide as the biologically active lipid, PEG as the lipopolymer, and phosphatidylcholine as the phospholipid in the reply filed on 18 May 2009 is acknowledged. The traversal is on the ground(s) that there is unity between said species. This is not found persuasive due to the reason shown above in part I.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-8, 10-11, 13-14, 16 and 26 are under examination.

### *Information Disclosure Statement*

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

### *Claim Objections*

Claims 2, 4-8 and 14 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. It is unclear if the lipid assembly of claim 1 further comprises a lipid matrix, or is in the form of a lipid matrix. Claims 2 and all claims dependent thereof will be examined as the lipid assembly is in the form of a lipid matrix, e.g., the lipid assembly of claim 1 comprises a phospholipid.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the limitation “at least about." The term “at least” delineates only numerical values more than the recited value where the term “about” may be less than or more than the recited value. Because of the conflict of terms, it is unclear which term is limiting. See also MPEP 2173.05(b) (citing Amgen v. Chugai, 18 USPQ2d 1016 (Fed. Cir. 1991), in which the phrase “at least about” was held indefinite).

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The structure diagram that is shown in claim 6 shows R1, R2, and R, whereas the claims define R1, R2, and R3. R3 is not shown in the structure, and R is not defined by the claims. The examiner will examine the claims as if R is R3.

Claims 11 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 depends upon cancelled claim 9, and is therefore indefinite. Claim 16 depends upon cancelled claim 12, and is therefore indefinite. Claim 11 will be examined as if it depends upon claim 10, and claim 16 will be examined as if it depends upon claim 14.

***Claim Rejections - 35 USC § 103***

Claims 1-2, 4-5, 10, 14, 16 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al. (US 5,677,337) as evidenced by Kumar (as admitted by applicant).

Wei, Example 7 (column 17 lines 16-20 and column 18 lines 1-10), teaches liposomal formulations of C2 and C6 ceramides. Tables 5 and 6 further show that liposomes were prepared with free, non-silylated C6 ceramides as well as silylated C6 ceramides. The examiner directs applicant to Figures 2a-2d for the structures of said ceramides. Said structure reads on the additional limitations of claim 5. The liposome of Wei includes phosphatidylcholine (see Wei, column 15 Example 1, wherein example 7 refers back to example 1 on column 18 line 4). Phosphatidylcholine reads on the additional limitations of claims 14 and 16.

The specific combination of features claimed is disclosed within the broad generic ranges taught by the reference but such "picking and choosing" within several variables does not necessarily give rise to anticipation. Corning Glass Works v. Sumitomo Elec., 868 F.2d 1251, 1262 (Fed. Circ. 1989). Where, as here, the reference does not provide any motivation to select this specific combination of variables anticipation cannot be found. Such variables, as taught by Wei, include the following: Wei teaches, in column 13 lines 41-45 and column 13 line 67-column 14 lines 1-3, the a lipopolymer (of instant claim 1), wherein said lipopolymer comprises a headgroup modified lipid, wherein said headgroup may be selected from a group that includes polyethylene glycol. Wei, column 14 lines 41-50 teaches the use of said liposome with a

pharmaceutically acceptable carrier (as of instant claim 26). Wei column 1 lines 10-15, teaches that the achieved biological effect is in regards to treating cancer.

That being said, however, it must be remembered that "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". KSR v. Teleflex, 127 S,Ct. 1727, 1740 (2007) (quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976)). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (Id.). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is… a person of ordinary creativity, not an automaton." Id. at 1742.

Consistent with this reasoning, it would have obvious to have selected various combinations of various disclosed ingredients, which are a lipopolymer and a pharmaceutically acceptable carrier, from within a prior art disclosure, to arrive compositions "yielding no more than one would expect from such an arrangement".

Wei does not teach that the lipid assembly is stable at 4 C for six months.

However, the stability of the lipid assembly at 4 C for six months would be an expected property of a lipid assembly consisting of ceramide and a pegylated lipid, as there are no oxidatively labile groups in ceramide, and it is shielded due to the presence of PEG. PEG reads on the additional limitation of claim 10. The examiner points to page 71 first full paragraph of the specification which shows that PEG causes the stabilization of lipid assemblies.

Wei does not teach that the biologically active lipid has an atomic mass ratio of hydrophobic to hydrophilic region that is less than 0.3

However, the mass ratio of less than 0.3 of the polar headgroup and hydrophobic region is an expected property of ceramide (as in Figure 1), as the polar headgroup contains approximately five polarized non-hydrogen atoms (four hetero-atoms and a carbonyl carbon) and approximately 22 hydrophobic carbons among both tails, resulting in a molecular weight ratio of approximately 5/22, which is less than 0.3. Furthermore, the instant specification, page 32 Table 2A and page 33 table 2B, utilize C2 and C6 ceramides as biologically active lipids.

Wei does not specifically teach that the additive packing parameter of the lipid assembly is between the range of 0.74 and 1, as of instant claim 2.

An additive packing parameter in the range of 0.74 to 1 is an expected property of the composition formed combining pegylated lipids and ceramide to form a liposome. This argument is made as evidenced by Kumar, (page 447, left column, first paragraph of discussion section), which shows that the value of S (wherein S is the additive packing parameter) should be 0.74 or greater for lipid assemblies with a bilayer. Wei,

Example 7 teaches liposomes, which comprise a bilayer, therefore it is expected that said liposomes have an additive packing parameter greater than 0.74. Kumar, page 447 right column second full paragraph, also teaches that the additive packing parameter cannot exceed 1. The examiner further points out that the instant specification teaches that amphipiles with a packing parameter of about 1.0 form a lamellar phase and have the potential to form liposomes, which comprise bilayers.

Wei does not teach that the biologically active lipid has a packing parameter greater than 1.

It is an expected property of C6 ceramide that said packing parameter is greater than 1, because ceramides have small headgroups. Therefore, ceramides pack tightly, resulting in a packing parameter that is larger than 1, as of the instant specification, page 5 second full paragraph.

Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al. (US 5,677,337) as applied to claim 5 above, and further in view of Cuvillier et al. (Nature, June 27 1996, 381, p. 800-803).

Wei, column 17 Example 7, lines 15-19 and column 18 lines 1-10, teaches a liposomal formulation comprising ceramides. Wei column 1 lines 10-15, teaches that the achieved biological effect is in regards to treating cancer.

Wei does not teach an embodiment wherein the biologically active lipid is N,N-Dimethylsphingosine, as of instant claims 6-8.

Cuvillier et al. teaches, on page 802 Figure 3C, that N,N-dimethylsphingosine (DMS) causes DNA fragmentation in the absence of SPP (a compound used to protect cells from apoptosis). Also see Cuvillier, page 800, right column, last line of column.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined DMS to the liposomal formulation of Wei. This is because, according to Cuvillier, page 800, right column, last line, DMS destroys DNA and thereby promotes apoptosis. This renders DMS useful in preventing the spread of proliferative diseases (e.g. cancer) by causing said proliferating cells to undergo apoptosis, thereby improving the liposomes of Wei to more effectively treat cancer. One of ordinary skill in the art would have been motivated to use DMS as an active agent to target cancer.

Claims 3, 11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wei as applied to claim 1 above, and further in view of Nicholas et al. as evidenced by Tirosh et al.

Indefinite claim 11 will be examined as if it depends upon claim 10.

Wei, Example 7 (column 17 lines 16-20 and column 18 lines 1-10), teaches liposomal formulations of C2 and C6 ceramides. Tables 5 and 6 further show that liposomes were prepared with free, non-silylated C6 ceramides as well as silylated C6 ceramides. The examiner directs applicant to Figures 2a-2d for the structures of said ceramides. Said structure reads on the additional limitations of claim 5. The liposome of Wei includes phosphatidylcholine (see Wei, column 15 Example 1, wherein example 7

refers back to example 1 on column 18 line 4). Phosphatidylcholine reads on the additional limitations of claims 14 and 16.

Wei does not teach liposomes with pegylated lipids wherein the molecular weight of PEG is 2000 Daltons, as of claims 11 and 12.

Nicholas, page 168, right column, section 2.2 teaches the formation of a liposome with PEG of a 2000 Dalton molecular weight.

It would have been prima facie obvious for one of ordinary skill in the art to have modified the liposome as taught by Wei et al. to further include PEG lipids in view of the teachings of Nicolas. One would have been motivated to do so because pegylated lipids stabilize liposomes, as according to Nicholas, page 167 left column, and further, PEG forms stealth liposomes to evade clearance by the body. Furthermore, it would have been prima facie obvious for one of ordinary skill in the art to have optimized the molecular weight of PEG, as said molecular weight affects the structure of the liposome, which therefore affects its permeability. This is shown by Nicholas, page 167, right column, and page 168, left column, top two paragraphs.

Nicholas does not disclose that there are 60 molecules of water per lipopolymer headgroup, as of claim 3.

That there are 60 water molecules per lipopolymer headgroup is an expected property of a lipopolymer comprising a PEG headgroup of 2000 Daltons. Tirosh, Table 1 page 1373, right column, bottom, shows that there are about 200-210 water molecules per headgroup in regards to micelles comprising PEG-2000, and approximately such a number of water molecules per headgroup would be expected for liposomes.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/I. S./
Examiner, Art Unit 1612

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642